UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SOUTHERN RESEARCH INSTITUTE and GENYZME CORPORATION, Plaintiffs, v. ABON PHARMACEUTICALS LLC, Defendant.	HONORABLE JOSEPH E. IRENAS CIVIL ACTION NO. 12-4709 (JEI/KMW) **CLAIM CONSTRUCTION OPINION**

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IRENAS, Senior District Judge:

This is a patent infringement case brought under the Hatch-Waxman Act. Plaintiffs Southern Research Institute and Genzyme Corporation allege that Defendant Abon Pharmaceuticals LLC ("Abon") has infringed U.S. Patent No. 5,661,136 (the "'136 patent"). Presently before the Court is the parties' request for claim construction. The Court held a *Markman* hearing on August 13, 2013, and now construes the disputed claim terms as set forth below.

I.

Plaintiff Southern Research Institute ("Southern Research") discovers and develops drugs and then licenses them to pharmaceutical companies. Plaintiff Genzyme Corporation ("Genzyme") is a pharmaceutical company that manufactures and markets treatments for various rare diseases as well as multiple sclerosis. One of the products that Genzyme manufactures is Clolar, a drug indicated for the treatment of pediatric patients with lymphoblastic leukemia who have not been cured by other

therapies. Clolar's active ingredient is clofarabine, which is a purine nucleoside compound. Clofarabine's chemical name is 2-Chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9H-purin-6-amine. The '136 patent covers methods of using nucleosides, including clofarabine, as cytotoxic compounds in mammalian cells. Southern Research is assigned the '136 patent and has licensed it exclusively to Genzyme.

Clolar is indicated to treat pediatric patients aged one to twenty-one years old suffering from acute lymphoblastic leukemia ("ALL") who have already undergone at least two unsuccessful treatments. ALL is a cancer of the bone marrow and bone that starts in the lymphoblasts. There are approximately 6,000 new cases each year in the United States. Clolar is administered through an intravenous solution.

Clofarabine works by causing cell death—or a cytotoxic effect—in both proliferating and quiescent cancerous cells. It does this in two ways. First, clofarabine inhibits DNA synthesis in cancerous cells. Second, it weakens the cells' mitochondrial membranes, which causes the cells to release their proteins. Clofarabine is a nucleoside analog, which means that it is similar to a naturally occurring nucleoside. Nucleosides are the building blocks of DNA and RNA; they also have functions in other cellular processes.

Because nucleosides serve so many functions, the human body screens out nucleoside analogs that are too different from natural nucleosides. But nucleoside analogs that are too similar to natural nucleosides can interrupt cellular processes and thus be ineffective as drugs. There are only a few dozen nucleoside analogs that the FDA has deemed safe and effective enough for use in human patients.

The ’136 patent has twelve claims covering methods of using certain nucleoside analogs to cause cell death and inhibit DNA and RNA synthesis in mammalian cancer cells. Clofarabine is one of the nucleoside analogs covered by the patent.

Defendant Abon Pharmaceuticals has filed an abbreviated new drug application (“ANDA”) seeking to market a generic version of clofarabine. In its application, it argued both that its generic would not infringe the ’136 patent and that the ’136 patent is invalid. In response, Plaintiffs filed this action for patent infringement.

The parties have identified two claim terms that require construction: “a cytotoxic effect in a mammalian cancerous cell” and “inhibiting ribonucleotidereductase and DNA polymerase α in a mammalian cell.” The Court construes these claims below.

II.

Claim construction is a matter of law for the Court to decide. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996). "It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1319 (Fed. Cir. 2005) (en banc) (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1115 (Fed. Cir. 2004)).

The Court begins a claim construction analysis by examining the intrinsic evidence, which includes the claims, the specification, and the prosecution history.[1] *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "A claim construction analysis must begin and remain centered on the claim language itself." *Innova*, 381 F.3d at 1116. There is a heavy presumption that a claim term conveys its ordinary and customary meaning, which "is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips*, 415 F.3d at 1313. But a patentee may overcome this presumption and choose "to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term." *Johnson Worldwide Assocs., Inc.*

[1] The prosecution history "consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent." *Phillips,* 415 F.3d at 1317.

v. Zebco Corp., 175 F.3d 985, 990 (Fed. Cir. 1999); *see also Schering Corp. v. Amgen Inc.,* 222 F.3d 1347, 1353 (Fed. Cir. 2000); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979–80 (Fed. Cir. 1995), *aff'd* 517 U.S. 370 (1996).

The claims themselves and the context in which a term is used within the claims can "provide substantial guidance as to the meaning of particular claim terms." *Phillips,* 415 F.3d at 1314. In addition, other claims of the patent may be useful in construing a claim term, as "claim terms are normally used consistently throughout the patent." *Id.* Similarly, claims that differ from each other may provide insight into how a term should be read. *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1538 (Fed. Cir. 1991).

After examining the claims, "it is always necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning." *Vitronics*, 90 F.3d at 1582. "For claim construction purposes, the description may act as a sort of dictionary, which explains the invention and may define terms used in the claims." *Markman*, 52 F.3d at 979. For this reason, "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Vitronics*, 90 F.3d at 1582.

Finally, the Court should also examine the prosecution history, if it is in evidence. *Phillips*, 415 F.3d at 1317. "The prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.*

"[I]deally there should be no 'ambiguity' in claim language to one of ordinary skill in the art that would require resort to evidence outside the specification and prosecution history." *Markman*, 52 F.3d at 986. But if the term remains unclear or unambiguous after examining the intrinsic evidence, the Court may turn to extrinsic evidence. *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1216 (Fed. Cir. 1995). "Extrinsic evidence consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980. Although extrinsic evidence is useful in determining how a person of ordinary skill in the art would understand the term, it is less reliable for the purposes of claim construction than the patent and its prosecution history. *Phillips*, 415 F.3d at 1318-19. Therefore, extrinsic evidence must be viewed within the context of intrinsic evidence. *Id.* at 1319.

III.

The parties have asked the Court to construe two terms. The first term is "a cytotoxic effect in a mammalian cancerous cell." It appears in claims 1, 3, 4, and 5 of the '136 patent. Plaintiffs ask the Court to give the term its plain and ordinary meaning, which they argue is "toxicity to cancerous cells in, or derived from, a mammal (such as a human)." Abon, on the other hand, argues that this term restricts the claim to the treatment of cells *in vitro* and *in vivo*. Its proposed construction is as follows: "a cytotoxic effect in a mammalian cancerous cell *in vitro* or *in vivo* in laboratory animals."

The second term is "inhibiting ribonucleotidereductase and DNA polymerase α in a mammalian cell." This term appears in claims 6, 8, 9, 11, and 12. Plaintiffs ask the Court to give this term its plain and ordinary meaning and offer the following construction: "inhibiting the activity of the ribonucleotidereductase and DNA polymerase α enyzmes in cells in, or derived from, a mammal (such as a human)." Abon asks the Court to construe the claim as follows: "inhibiting ribonucleotidereductase and DNA polymerase α in a mammalian cell *in vitro* or *in vivo* in laboratory animals."

The parties' main dispute is whether "mammalian cancerous cell" and "mammalian cell" are understood to include hosts, such

as humans, outside of a laboratory setting.[2] Plaintiffs argue that these terms encompass humans, while Abon argues that they do not. Although both parties rely on the claims and specifications to support their arguments, the crux of the issue is whether the applicants disclaimed treatment of humans in their statements to the examiner during prosecution.

A.

The claim language itself does not contain any restriction to mammalian cells in a laboratory. It is also clear from the language in the specifications that a person having ordinary skill in the art would understand the claims to encompass treatment of cancer in humans. The specifications contain several references to therapeutic administration and pharmaceutically acceptable salts. *See, e.g.*, '136 Patent, col. 11, ll. 20, 23-29, 33, 36, 56-60, 62. In addition, the specifications discuss the invention's utility in killing cancer cells in humans, *id.* col. 8, ll. 14-17, as well as the proper dosage for humans. *Id.* col. 11, ll. 10-65.

Abon argues that the fact that all of the examples were performed either *in vitro* or *in vivo* in cells implanted in mice indicates that the claims are not directed towards the treatment

[2] As the considerations in construing both terms are substantially similar, the Court will address them together.

of humans. But this argument is unavailing. The law is clear that "even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using 'words or expressions of manifest exclusion or restriction.'" *Liebel-Flarsheim Co. v. Medrad, Inc.*, 385 F.3d 898, 906 (Fed. Cir. 2004) (quoting *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F3d 1313, 1327 (Fed. Cir. 2002)). The specifications contain no such intention. Thus, because the claims and specifications counsel a construction that encompasses human treatment, the Court turns to the prosecution history.

B.

Abon argues that its construction should prevail because the applicants disclaimed treatment of humans during the prosecution of the '136 patent. Plaintiffs counter that as the examiner never accepted the applicants' arguments, their statements should not be treated as a disclaimer.

The prosecution history of the '136 patent is complicated and spans two patent applications, U.S. Patent Application Serial Nos. 07/693,646 ("the '646 application") and 08/320,879 ("the '879 application"). The '879 application was a continuation of the '646 application. The '646 application

issued as U.S. Patent No. 5,384,310 ("the '310 patent"), which is not at issue in this case. Originally, the '646 application included claims to methods of using clofarabine, but those claims were cancelled from the '646 application and prosecuted in the '879 application.

The parties agree that the applicants made several statements denying that the claims covered human treatment to the patent examiner during the prosecution of the '310 and '136 patents. The applicants made these statements in response to the examiner's repeated rejection of the claims for lack of utility and enablement.

In his rejection of the method claims in the '646 application, the examiner stated that the applicants had not provided enough data to show that "the instant claimed subject matter includes efficacious application to human subject suffering from 'cancer.'" (Gannon Cert. Ex. 12, at 2) The examiner also stated, "[T]he term 'mammalian' is directed to a vast array of cells both in culture and in specific hosts. Applicant [ha]s not further limited the host or the particular conditions to be treated under the generic umbrella of said term . . . . [A]pplicant has failed to specify that the 'mammalian cells' are in need of treatment and hence the instant claims read on the treatment of a well person." (*Id.* at 3) He noted, "[A]pplicants have provided no support for the

administration of said compound to any single host in their specification and hence the term 'mammal' which would include humans is not supported." (*Id.* at 5)

In reply, the applicants argued that the claims "are not directed to claiming application to human subjects suffering from cancer," but rather "are clearly directed to a method for bringing about a cytotoxic effect in a mammalian cancerous cell." (Gannon Cert. Ex. 7, at 8). They also stated, "Applicants have provided a limitation which the Examiner has not appreciated. The claim language is clear in that it does not encompass a method for inhibiting [ribonucleotide reductase and DNA polymerase α] in any fish, mouse, rabbit, human, horse, dog, or zebra host; the claim language is limited to a method for inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell." (*Id.* at 11) The applicants made several similar statements throughout their response.

Despite these statements, the examiner again rejected the method claims on the same bases in a January 7, 1993 Office Action, noting that the claims lacked utility and were not enabled for human subjects. (Gannon Cert. Ex. 13, at 5-9) The applicants again stated that the claims were not directed to a method of treatment of human subjects. (Gannon Cert. Ex. 8, at 5-7, 8-9, 12-14) The examiner deemed these statements unpersuasive and issued a final rejection on October 22, 1993.

(Gannon Cert. Ex. 14) At that point, the applicants cancelled all of the method claims (Gannon Cert. Ex. 9), and the ’310 patent issued on January 24, 1995, with claims directed to the nucleoside analog compounds and pharmaceutical compounds. (Gannon Cert. Ex. 15)

Following the issuance of the ’310 patent, the applicants filed the ’879 application and again attempted to pursue the method claims to “bringing about a cytotoxic effect in a mammalian cancerous cell” and “inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell.” (Gannon Cert. Ex. 10)

On February 15, 1995, the examiner once again rejected these claims for lack of enablement because they did not show a therapeutic effect in humans suffering from cancer: “Applicant’s specification fails to provide sufficient guidance or support to enable the worker of ordinary skill in the art to use the active ingredients as alleged, the administration of the instant pharmaceutical compositions to higher mammalian hosts in need of treatment for cancer, e.g. in humans.” (Gannon Cert. Ex. 16, at 3) The examiner further stated, “The mere statements that the compounds of the instant invention are likely to be effective in human hosts, or expected to be effective, are insufficient to enable the worker of ordinary skill in the art

to practice the invention." (*Id.*) He also noted that the applicants' response to his objects was unpersuasive.

The applicants responded to the examiner's objections in an Amendment dated May 15, 1995. In that document, the applicants clarified that "the specification is not for the treatment of a disease." (Gannon Cert. Ex. 17, at 6) They insisted that the compounds were not intended for therapeutic use. (*Id.* at 7-10) Despite these arguments, on July 21, 1995, the examiner remained unconvinced and issued a final rejection of the claims on the exact same grounds as before. (Gannon Cert. Ex. 18) The applicants then submitted an Amendment after Final on October 23, 1995, in which they stated, *inter alia*, "The compounds have not been described as therapeutics for the treatment of cancers in human patients." (Gannon Cert. Ex. 19, at 3)

During a telephone interview with the applicants' attorney on November 6, 1995, the examiner advised the applicants that "the breadth of the claims (treating all cancers) was deemed to be too broad in view of the showing of efficiacy [sic] against only a single strain of leukemia in mice." (Gannon Cert. Ex. 20) He informed the applicants' attorney that limiting the claims to leukemia would correct the problem. There was no mention of the dispute about therapeutic treatment of humans.

The applicants then submitted a Supplemental to Amendment after Final on November 7, 1995. (Gannon Cert. Ex. 21) In that

document, the applicants provided additional data that showed clofarabine's efficacy against several kinds of cancers *in vitro* and *in vivo*, including leukemia, breast cancer, colon cancer, and lung cancer. This document did not contain any statements that the claims did not cover treatment of humans. On November 14, 1995, the examiner issued a Notice of Allowability for all of the claims. In that notice, he pointed to the November 6 interview summary record. The '136 patent issued on August 26, 1997.

Abon argues that the applicants' clearly disclaimed a therapeutic use for humans during the prosecution of the '310 and '136 patents. Plaintiffs counter that these statements cannot act as a disclaimer because the patent examiner never accepted the applicants' disclaimers and the applicants ultimately adopted the examiner's view that the claims covered treatment of humans. The Court agrees with Plaintiffs.

The doctrine of disclaimer prevents applicants from recapturing specific meanings in the claim construction process that they expressly disclaimed during prosecution. *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003). Because the prosecution history serves a public notice function, this doctrine allows the public to rely on statements made during prosecution. *See Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1347 (Fed. Cir. 1998). Thus, "an

applicant's statements to the PTO characterizing its invention may give rise to a prosecution disclaimer." *Uship Intellectual Props., LLC v. United States*, 714 F.3d 1311, 1315 (Fed. Cir. 2013). However, a disclaimer must be clear and unambiguous to preclude that interpretation during claim construction. *Omega Eng'g*, 334 F.3d at 1324. "[I]t is the totality of the prosecution history that must be assessed, not the individual segments of the presentation made to the Patent and Trademark Office by the applicant . . . ." *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 979 (Fed. Cir. 1999).

Looking at the whole of the prosecution history in this case, the applicants' statements do not constitute a disclaimer. While it is true that the focus in analyzing whether a disclaimer occurred is on the applicants' statements, not the examiner's, this case is unique. Although applicants indicated that the claims did not cover human treatment, the examiner consistently rejected their interpretation.

Over the course of two patent prosecutions, both involving several amendments, the examiner never once accepted the applicants' understanding of the claims and in fact explicitly rejected the applicants' position. *Cf. Abbott Labs. v. Church & Dwight Co., Inc.*, No. 07-3428, 2008 WL 5387848, at *8 (N.D. Ill. Dec. 22, 2008) ("[W]hen the PTO expressly rejects an applicant's proposed construction, . . . the public presumably is aware that

despite an applicant's statements to the contrary, the patent claim in question has a different construction.").

In addition, there is evidence that the applicants acquiesced in the examiner's understanding. First, even faced with the examiner's repeated insistence that the claims as worded covered treatment of humans suffering from cancer, the applicants never once amended their claims to exclude human treatment to overcome his objections.[3] Second, the examiner's description of the phone interview on November 6 indicates that the applicants agreed that the claims covered treatment. The examiner stated that he informed the applicants' attorney that "the breadth of the claims (**treating all cancers**) was deemed to be too broad" in light of the fact that the only data presented

[3] It bears repeating that this situation is unique. Apart from the applicants' statements during the prosecution, nothing about these circumstances or the '136 patent indicate that the claims were not directed to treatment of humans. The applicants — who unquestionably are in the business of researching treatments for human diseases — submitted an application whose central claims quite obviously cover the treatment of humans suffering from cancer. The patent examiner saw this and informed the applicants that the claims clearly did speak to human treatment. In doing so, the examiner recognized not only that such a reading of the claims was central to the patent but also that a person having ordinary skill in the art would understand the claims to apply to treatment of human subjects. Rather than amending their claims to exclude treatment of humans, which they easily could have done, the applicants repeatedly told the examiner that human subjects were outside the scope of the claims. If the claims at issue were not central to the purpose of the patent, the lack of any amendment could be overlooked. But in this case, the disputed terms are the core of the patent, and the applicants chose to leave the claims in a context that covered treatment of humans.

Where the claim language is truly ambiguous or the claim is dependent on the earlier claims, simply disclaiming a particular construction might be enough to preclude that meaning at a later date. But where, as in this case, the disputed claims form the essence of the patent and the claim language in the Court's view is unambiguous, a disclaimer, repeatedly rejected by the examiner, is not enough to negate the terms' plain meaning without amending the terms.

related to leukemia. (Gannon Cert. Ex. 20 (emphasis added)) Thus, at the time of the interview, the only remaining issue was whether all cancers were covered given the data provided. The examiner's use of "treating all cancers" also suggests that the applicants had accepted this understanding of the claims.

Third, in their Supplement to Amendment to Final, the applicants made no mention of the exclusion of treatment of human subjects and instead focused on providing information about the compound's efficacy in treating other forms of human cancers. Taken together, these facts demonstrate that the applicants acquiesced to the examiner's understanding. As such, the applicants' statements do exclude treatment of humans. *Cf. Spring Window Fashions LP v. Novo Indus., L.P.*, 323 F.3d 989, 995 (Fed. Cir. 2003) (holding that the disclaimer doctrine applied in part because the applicant did not "acquiesce in the examiner's comments" but rather continued to oppose the examiner's interpretation).

C.

The Court thus construes the disputed terms in light of its finding that the applicants did not disclaim treatment of humans and adopts Plaintiffs' constructions. The Court therefore gives "a cytotoxic effect in a mammalian cancerous cell" the following construction: "toxicity to cancerous cells in, or derived from,

a mammal (such as a human)." The Court construes "inhibiting ribonucleotide reductase and DNA polymerase α in a mammalian cell" as follows: "inhibiting the activity of the ribonucleotide reductase and DNA polymerase α enzymes in cells in, or derived from, a mammal (such as a human)."

IV.

For the reasons set forth above, the disputed claim terms will be construed as indicated. An appropriate Order accompanies this Opinion.

Date: August 22, 2013

/s/ Joseph E. Irenas

Joseph E. Irenas, S.U.S.D.J.